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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROGERS, JAMES WILLIAM	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,045	CHAU ET AL.	
	Examiner	Art Unit	
	James W. Rogers, Ph.D.	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-23,29,33,39 and 43-56* is/are pending in the application.

4a) Of the above claim(s) *24-28,30-32,34-38 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-14,17-22,29,33,39,43,44,47-52 and 54-56* is/are rejected.

7)☒ Claim(s) *15,16,23,45,46 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/03/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any rejection/objection from the previous office action dated 04/11/2006 not addressed in the office action below have been withdrawn. The Sequence Listing filed 12/18/2006 has been entered. The amendments to the claims filed 10/16/2006 have been entered.

Election/Restrictions

Applicant's election without traverse of the species matrix metalloproteinase II in the reply filed on 12/18/2006 is acknowledged. Claims 1-6,9-23,29,33,39 and 43-56 read on the elected species, all other claims have been either cancelled or withdrawn by applicants.

Claim Objections

Claims 15-16,23,45-46 and 53 are objected to for depending upon rejected claims. If the dependent claims were rewritten to include the limitation of the claims above and rewritten to overcome the 35 USC § 112 rejections they would be in condition for allowance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Regarding claims 1 and 12-13 while there is written support for the specific oligopeptide linkers IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2 there is no written support for oligopeptide linkers that are cleavable by serine proteases or matrix metalloproteases. Note that the species MMP-2 does not define the genus of metalloproteases recited in claims 1 and 12-13. Regarding claim 2 while there is support for a plurality of drugs for use in the drug conjugate there is no written support that more than one type of linker may be used on the same drug conjugate. It is suggested by the examiner that applicants delete the recitation of "additional linkers" from claim 2.

Claims 1-2 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a for the oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2, does not reasonably provide enablement for a linker that is cleaved when the conjugate is exposed to a digestive enzyme selected from the group consisting of serine proteases and matrix metalloproteinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Also claims 1-2 and 12-13 can be considered reach through claims because the claims as currently recited would read on oligopeptide sequences cleavable by serine proteases and matrix metalloproteases yet to be discovered or identified.

The instant claims are drawn to a conjugate for targeting a drug to a tissue comprised of a polymeric carrier, a drug molecule and an oligopeptide linker. The instant specification fails to provide information that would allow the skilled artisan to practice the prevention of the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to a conjugate for targeting a drug to a tissue comprised of a polymeric carrier, a drug molecule and an oligopeptide linker linking the drug and polymeric carrier.

(2) The breadth of the claims:

Claim 1 embraces a conjugate comprised of a polymeric carrier a drug molecule and a linker between the drug and carrier, the linker reads on any peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and

matrix metalloproteinases. The specification only enables a linker comprised of the following oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2.

(3) The state of the prior art:

The state of the art regarding drug conjugates comprising peptide linkers cleavable by select enzymes is high. However, the state of the art for using peptide linkers cleavable by any digestive enzyme is very low or does not exist. This is verified by applicants own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences". Thus the skilled artisan must carefully select a peptide that is cleavable by a select digestive enzyme, a select digestive enzyme will not cleave any peptide sequence because the digestive enzyme is very selective.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to other peptide linkers besides the oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2 is completely lacking. The specification as filed does not speak on or show any

working examples or any studies performed on other cleavable peptide sequences. The specification only enables the linker to be selected from the specific oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2. In each example, only the previous sequences are provided, guidance on the use of other peptide linkers and the enzymes which cleave those peptide linkers is not provided. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on a conjugate comprised of a polymeric carrier, a drug molecule and a linker between the drug and carrier, the linker reads on any peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and matrix metalloproteinases. As discussed above the specification fails to provide any support for the use of peptide linkers besides the oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the specification is enabled for linkers comprised of the following oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2, but is not enabled for any linker comprising a peptide or protein capable of being cleaved by digestive enzymes selected from serine proteases and matrix metalloproteinases. It is suggested by the examiner to include the specific peptide sequences above into the dependent claims to remove this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,4-5 and 12-13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claims 1,4 and 12-13 the limitation that the drug is a "drug molecule" or a "small molecule drug" or a "biomolecular drug" are all extremely broad, so broad in fact that one with adequate skill in the art would not be reasonably apprised of the scope of the invention as to the types of drugs useful in the invention. It is suggested by the examiner that applicants limit their claims to a specific specie(s) supported in the specification such as doxorubicin. Specifically in claim 4 the recitation that the size of the polymeric carrier is larger than the renal excretion limit is indefinite. The phrase "size of the polymeric carrier is larger than the renal excretion limit" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention as to the size of the polymeric

carrier. It is suggested by the examiner to delete the phrase "size of the polymeric carrier is larger than the renal excretion limit". The examiner suggests limiting the size of the polymeric carrier by a MW range supported in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6,9-13,17-22,29,33,39,43,47-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Copland et al. (WO 01/68145 A2).

Copeland discloses antineoplastic agents such as doxorubicin conjugated to enzyme-cleavable peptides comprising amino acid recognition sequences and the use of such agents in the targeted treatment of cancers. The enzyme-cleavable peptides included (MMP) recognition segments such as MMP-2. See abstract, pag 2 lin 15-pag 3 lin 32, pag 17 lin 8-pag 21 lin 14 and pag 53 lin 3-30. Regarding the limitation in claims 1,12 and 13 on a polymeric carrier, The Copeland patent specifically mentions that enzyme cleavable peptide can be substituted with a capping group such as PEG. See pag 42 lin 19-pag 43 lin 20. Also since the enzyme selective peptide sequences are sequences in a larger polypeptide the rest of the peptide not cleaved by the digestive enzyme can be considered as a polymer carrier, since peptides are poly amino acids. Regarding claim 17 Copeland specifically mentions that the pharmaceutical compositions also include a pharmaceutically acceptable carrier. See pag 47 lin 23-31.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6,9-14,17-22,29,33,39, 43,44,47-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being unpatentable by Duncan et al. (WO 98/56425, cited in last office action) in view of Copeland et al. (WO 01/68145 A2).

Duncan discloses prodrugs and the method to make them; the prodrugs are activatable by digestive enzymes (injected before or after in the tissue, thus they are over-expressed in that area), in which the drug (including doxorubicin and methotrexate) is connected covalently to a linker (including peptides), which is further connected to a hydrophilic polymer (including dextran). See abstract, page 6 lin 22-33, page 8 lin 34-page 9 lin 22, page 10 lin 10-11, page 11 lin 15-27 and claims 2-4. Regarding claims 9,10 and 13 Duncan used the prodrugs to treat mice with tumors. See page 8 lin 34-page 9 lin 22 and ex. 1-2. Regarding claim 11 Duncan specifically claims a pharmaceutical composition comprising an excipient (claim 17). Regarding claims 54-56 since the active ingredients of the pro-drugs within Duncan are the same as the actives claimed by applicants they will have the same effects when administered to a subject in need. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case or either anticipation or obviousness has been established, Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Copeland discloses antineoplastic agents such as doxorubicin conjugated to enzyme-cleavable peptides comprising amino acid recognition sequences and the use of such agents in the targeted treatment of cancers. The enzyme-cleavable peptides included (MMP) recognition segments such as MMP-2. See abstract, pag 2 lin 15-pag 3 lin 32, pag 17 lin 8-pag 21 lin 14 and pag 53 lin 3-30.

It would have been prime facie obvious at the time of the invention to a person of ordinary skill in the art to modify the peptide linkers disclosed in Duncan and add the peptide sequences disclosed within Copeland. The motivation for combining them would be to produce a drug conjugate comprising a chemotherapeutic drug such as doxorubicin or methotrexate linked to a polymeric carrier such as dextran through an oligopeotide linker cleavable by MMP-2. It would have been obvious to one skilled in the art that the peptide sequences within Copeland could be incorporated within the Duncan patent because the linkers are related in that they are used to target tissue and are cleavable by digestive enzymes thus the peptides are related in their use and function. The advantage of modifying the linkers of Duncan with the MMP-2 cleavable peptides within Copland would be that the that the prodrug would be targeted to tissue where MMp-2 is over expressed such as carcinomas tissue, thus the compounds are inactive or significantly less active upon administration to non-diseased tissue, thus lowering the toxicity. Thus, the claimed invention, taken as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 and 16 of copending Application No. 60/779401. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-13 are generic to all that is recited in claims 1-14 and 16 of copending Application No. 60/779401. That is, claims 1-14 and 16 of copending Application No. 60/779401 falls entirely within the scope of claims 1-13, in other words, claims 1-13 is anticipated by claims 1-14 and 16 of

copending Application No. 60/779401. Specifically the drug combination for claims 1-14 and 16 of Application No. 60/779401 is the same as the drug combination in claims 1-13.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER